Assessment of vascular patency and inflammation with intravascular optical coherence tomography in patients with superficial femoral artery disease treated with Zilver PTX stents

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Assessment of Vascular Patency and Inflammation with Intravascular Optical Coherence Tomography in Patients with Superficial Femoral Artery Disease Treated with Zilver PTX Stents

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ABSTRACT

Purpose: Zilver PTX nitinol self-expanding drug-eluting stent with paclitaxel coating is effective for treatment of superficial femoral artery (SFA) disease. However, as with any stent, it induces a measure of vascular inflammatory response. The current clinical trial (NCT02734836) aimed to assess vascular patency, remodeling, and inflammatory markers with intravascular optical coherence tomography (OCT) in patients with SFA disease treated with Zilver PTX stents.

Methods: Serial OCT examinations were performed in 13 patients at baseline and 12-month follow-up. Variables evaluated included neointimal area, luminal narrowing, thrombus area, stent expansion as well as measures of inflammation including, peri-strut low-intensity area (PLIA), macrophage arc, neovascularization, stent strut apposition and coverage.

Results: Percentage of malapposed struts decreased from 10.3 ± 7.9% post-intervention to 1.1 ± 2.2% at 12-month follow-up, but one patient showed late-acquired stent malapposition (LASM). The percent of uncovered struts at follow-up was 3.0 ± 4.5%. Average expansion of stent cross-sectional area from baseline to follow-up was 35 ± 19%. The average neointimal area was 7.8 ± 3.8 mm^2. Maximal luminal narrowing was 61.1 ± 25.0%, and average luminal narrowing was 35.4 ± 18.2%. Average peri-strut low-intensity area (PLIA) per strut was 0.017 ± 0.018 mm^2. Average number of neovessels per mm of stent was 0.138 ± 0.181. Average macrophage angle per frame at follow-up was 7 ± 11°. Average thrombus area at follow-up was 0.0093 ± 0.0184 mm^2.

Conclusion: At 12-month follow-up, OCT analysis of Zilver PTX stent shows outward remodeling and minimal neointimal growth, but evidence of inflammation including PLIA, neovessels, thrombus and macrophages.

Summary: Thirteen patients with PAD had paclitaxel-coated stents implanted in their SFAs and were then imaged with OCT at baseline and 12-month follow-up. OCT proxy metrics of inflammation were quantified.

Abbreviations: OCT, optical coherence tomography; PLIA, peri-strut low-intensity area; LASM, late-acquired stent malapposition; LST, late-stent thrombosis; DES, drug-eluting stent; PES, paclitaxel-eluting stent; EES, everolimus-eluting stent; SES, sirolimus-eluting stent.

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1. Introduction

Endovascular therapy (EVT) has evolved to the most effective method for the management of obstructive peripheral arterial disease (PAD) with progressive optimization of techniques and devices [1–3]. Primary nitinol stenting for superficial femoral artery (SFA) lesions is superior to balloon angioplasty alone with acceptable patency at 12 months. However, long term restenosis is a major limitation [3–5]. In an effort to reduce restenosis rates, a number of alternative EVT options have been developed, including atherectomy, drug-coated balloons, and drug-eluting stents (DES). Paclitaxel-coated DESs have achieved reduced restenosis and reintervention rates for patients with SFA disease [3–6].

Zilver PTX®, a paclitaxel-eluting nitinol stent (Cook® Medical, Bloomington, IN, USA) is approved by the Food and Drug Administration for use in femoropopliteal arteries. Previous studies have reported 5-year safety and efficacy of the Zilver PTX in patients with low de novo or restenotic lesions of the femoropopliteal artery [7,8]. However, late stent thrombosis (LST) after Zilver PTX implantation has also been reported [9]. In the coronary circulation, delayed vascular healing and incomplete endothelialization is associated with LST after first-generation drug-eluting stent (DES) implantation. These stents both delivered Paclitaxel and utilized a durable polymer as causes for delayed healing [10,11]. The Zilver PTX stent uses paclitaxel without polymer. A porcine study by Dake et al. [12] revealed that 95% of the stent paclitaxel was absorbed by the vessel and remained for 56 days, after which, it becomes a biocompatible bare metal stent [6].

Recently, a meta-analysis conducted by Katsanos et al. has found that the use of paclitaxel-coated devices in femoral and popliteal arteries is associated with a higher all-cause mortality than drug-free devices at 2- and 5-years [13]. This finding has resulted in the suspension of the BASIL 3, SWEDEPAD 1, and SWEDEPAD 2 clinical trials. Katsanos does not posit on the mechanism of death since the studies surveyed in his meta-analysis do not report cause of death. However, it can be hypothesized that the paclitaxel or its carrier could be responsible for these deaths. Zilver PTX has no carrier, allowing us to evaluate only the drug itself.

Various OCT features have been linked with the inflammatory response following stent implantation. Previous analyses have identified PLIA by OCT [6], and histological analyses have found analogous inflammation around struts of human autopsies [14,15]. This inflammatory presence has also been identified as PLIA in a porcine study [16]. Additionally, inflammatory cells such as macrophages and other leukocytes are associated with neovessel formation [17–19]. Human autopsy studies have found inflammation and uncovered struts to be jointly linked with acute myocardial infarction (AMI) [20,21]. Since poor strut coverage correlates with LST, and histopathological analysis of thrombus aspirates in LST patients suggests an inflammatory response leading to delayed endothelialization and persistent fibrin deposition [22], clot burden also serves as a proxy measurement of inflammation.

The current protocol originally was designed to assess the degree of stent expansion and malapposition in the SFA at baseline as well as late-stent malapposition and neointimal hyperplasia. Upon completing that analysis, we hypothesized that PLIA, neovessels, thrombus, uncovered struts, and LASM were all linked to paclitaxel-induced immune response.

2. Materials and methods

2.1. Study population

The Drug Eluting Stent for the management of PERipheral Arterial Disease Of the SFA (DESPERADO-SFA) study (NCT02734836) is a prospective, non-randomized, single-arm study using the Zilver PTX stent in patients with SFA disease (total occlusions or significant stenosis >60%). The primary inclusion criterion was the presence of claudication and/or critical limb ischemia with severe SFA disease on angiogram requiring percutaneous peripheral intervention (PPI). A total of 20 patients were consecutively enrolled in the study. The trial protocol was approved by the Western IRB (#20160494).

Inclusion criteria were: (I) Patients that are ≥18 years of age with lower extremity claudication and PAD due to significant SFA stenosis (60–99%) or total occlusions (100%) that affects the quality of life despite medical therapy; (II) Evidence of significant SFA disease involving the most symptomatic limb by noninvasive vascular testing with the use of the following: ABI: <0.9 (If ABI >1.4, SFA systolic acceleration time should be >140 milliseconds); toe brachial index: <0.6; computed tomographic angiography confirming at least a 60% SFA stenosis; or magnetic resonance angiography confirming at least a 60% SFA stenosis; (III) The patient was advised of the beneficial effects of smoking cessation and regular exercise without being in the process of changing their smoking status at the time of screening (patients could resume or increase exercising as an effect of post procedurally improved lower limb perfusion); (IV) Peak walking time limited only by claudication. Exclusion criteria included planned usage of atherectomy devices during procedure, planned amputation, any planned/scheduled revascularization procedures ≤30 days after baseline procedure, prior lower extremity revascularization ≤30 days before baseline procedure, in-stent restenosis (ISR), infra-popliteal disease involving the last remaining vessel, creatinine clearance <30 mL/min, bleeding disorders, active pathological bleeding, history of intracranial hemorrhage at any time, GI bleed in the past 6 months, or major surgery within the past 30 days. Known hypersensitivity to anti-coagulant, ischemic stroke during the past 3 months, severe liver disease, heart failure with an left ventricular ejection fraction <30%, risk of bradycardic events unless treated with a permanent pacemaker, female patients with known pregnancy, breastfeeding, or intent to become pregnant during the study period and concern for inability of the patient to comply with study procedures and/or follow up (e.g., alcohol or drug abuse).

OCT objectives of the analysis were the assessment of standard stent evaluation features including neointimal growth and stent expansion, as well as indicators of inflammation including neovascularization, macrophage content, thrombus burden, and strut malapposition and coverage. Clinical objectives were the assessment of patency (defined/evaluated by direct angiography and OCT imaging) of the target vessel, the measurement of ankle brachial index (ABI) and the Rutherford Class at baseline and at 12 months. Walking distance and target lesion revascularization were evaluated at baseline and at the 12th month follow up. Safety variables were distal embolization, puncture site complications, peripheral bypass and thrombosis.

2.2. Interventional procedure

We used a 6F sheath and the contralateral retrograde access approach after obtaining initial access using either an 18-gauge needle or a 21-gauge micro-puncture needle. The distal tip of the 6F sheath was placed in the common femoral artery (CFA) for imaging of the SFA. The target lesion was identified. Following peripheral angiography, patients with significant SFA disease (>60%) or total occlusions (100%) were treated with balloon angioplasty and stenting using the Zilver PTX stent. Balloon sizing was based on 1:1 vessel ratio with the length covering from minimally diseased distal segment to minimally diseased proximal segment. After pre-dilatation, appropriate stent deployment was performed. Stent diameter was based on the manufacturer's guidelines for vessel sizing (i.e., 1 to 2 mm stent: vessel oversizing). Stent length was based on covering the significant lesion completely from minimally diseased distal segment to minimally diseased proximal segment. An angiogram was performed to verify full deployment and expansion of the device; if there was incomplete expansion within the stent at any point along the lesion, post-deployment balloon dilatation was performed. OCT was performed to evaluate stent expansion and stent apposition as well as determination of intraluminal clot.

OCT images were acquired in each subject using commercially available, frequency domain (C7-XR™ OCT intravascular imaging system) St. Jude Medical™ OCT system. A 2.7- French (F) OCT imaging catheter (Dragonfly™, St. Jude Medical) was advanced into the distal lumen of the determined SFA segment and imaging was performed with an automated 20 mm/s, 54 mm diagnostic OCT pullback of the stented region, clearing the blood with a 40 mL power injection of clearing agent at 8 mL/s via side-arm of sheath. Blood was cleared with either dextran-40, iodixanol, or a 50:50 mixture of iodixanol:saline. If the stented length was >54 mm, multiple, overlapping pullbacks were performed to image the entire stent region.

All images were de-identified and digitally stored. Data were sent to the OCT core laboratory located at UT Health San Antonio, which was subcontracted to conduct the OCT analysis. OCT was the primary imaging method for the determination of optimal stent expansion and stent wall apposition along with the presence of intraluminal clot. The imaged vessel length was left to the discretion of the investigator as long as the entire stent segment and at least a short-uncovered vessel segment (distal and proximal to the stent, 5 mm minimum) was imaged. OCT imaging was repeated at 12 months. Patients were pre-loaded with 81 mg of acetylsalicylic acid and 300 mg of clopidogrel within 24 h prior to the peripheral intervention and continued with a once a day dosage of 81 mg of acetylsalicylic acid and a once a day dose of 75 mg of clopidogrel for 12 months. All adverse events were adjudicated by seriousness, severity, and causality. A hemoglobin drop>3 g/dL or hematoma at the groin >5 cm was considered serious adverse event.

An array of OCT features were collected throughout the stented region. Malapposition (at both baseline and follow-up) and strut coverage (at follow-up) were counted every 2 mm. Malapposed struts were defined as bright reflections positioned at least 200 μm from the luminal surface. Uncovered struts were defined as struts not covered by any neointimal tissue. Stent expansion from baseline and PLIA were measured every 1 cm. Neointimal area and luminal narrowing were measured every 1 mm. Luminal narrowing was defined as the ratio of the luminal cross-sectional area over the stent cross-sectional area at follow-up. Maximal luminal narrowing was defined as the luminal narrowing at the in-stent frame with the minimum lumen cross-sectional area for a patient. Maximal luminal diameter narrowing was defined similarly except in terms of diameter instead of area. To characterize the longitudinal distribution of the neointimal growth, the intra-patient standard deviation between cross-sections was calculated. Neovascularization frequency, macrophage angle, and thrombus volume were measured for every frame. A total of 26.14 cm of artery was stented, and 6.03 cm was excluded from follow-up analysis due to poor blood clearance, part of the vessel wall being outside the field of view of the OCT device, or a new stent being deployed in a segment at follow-up.

Angiography was exported as DICOM data and reviewed offline by the core lab. Stenosis assessment was measured with DICOM review and caliper software. The target lesion was defined as a region of narrowing containing a stenosis of >60%. The reference diameter was defined as the largest diameter within 10 mm of the lesion. Pre-procedural stenosis and residual stenosis were defined as the tightest narrowing of the vessel or stented vessel, respectively, with respect to the reference diameter.

2.3. Statistical analysis

Statistical analyses were performed using SPSS® 23 for Windows (SPSS Inc.®, Chicago, IL, USA). Distribution of data was assessed by using Shapiro–Wilk test. Numerical variables were presented as mean ± standard deviation, and categorical variables were presented as percentages. Paired sample *t*-test or Wilcoxon's signed-rank test was performed according to the normality of the variables. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical variables

A total of 20 patients were treated at Arkansas Heart Hospital with Zilver PTX for SFA lesions between April 2016 and June 2017; the last patient completed follow-up in June 2018. The average follow-up time of patients who completed the study was 12 months, 18 days. There were no serious adverse events and two minor complications were observed (femoral artery pseudoaneurysm in 1 patient and groin hematoma in 1 patient). Four patients withdrew their consent from the study after initial stenting, 1 patient could not be contacted, 1 patient died, and 1 patient was not properly imaged due to machine malfunction as well as the presence of total occlusion at follow-up that disqualified the patient from quantitative analysis. For the remaining 13 patients (mean age: 70.6 ± 10.3 years, 8 males), limbs (9 left and 4 right) were treated for life-disabling claudication with a total of 26 Zilver PTX (median number of stents per patient: 2, median stent diameter: 6 mm). One of the 13 had a drug-coated balloon used in the treated leg within 12 months before baseline imaging. Contralateral femoral arterial approach was used in 12 patients and ipsilateral retrograde popliteal artery approach was used in 1 patient. Serial OCT examinations were performed at 12-month follow-up. (See Fig. 1.) Two of the 13 patients required reintervention at follow-up after OCT imaging due to angiographic narrowing of the vessels. Clinical characteristics of study population are shown in Table 1. ABI ($p = 0.006$) and Rutherford classification ($p < 0.001$) improved at 12-month follow-up, and 6MWT did not ($p = 0.301$).

3.2. OCT endpoints

OCT data are shown in Table 2. Out of 13 patients who had follow-up OCT analysis, 11 had neovessels, 9 had PLIA, 8 had macrophage arcs, 6 had thrombus, and 1 had late-acquired stent malapposition.

4. Discussion

The major finding of this study was that twelve-month follow-up OCT imaging of SFAs stented with Zilver PTX revealed a number of OCT inflammatory markers which were not anticipated during study design. These included frequent neovessels (8 ± 10% of all frames), thrombus ($0.0093 \pm 0.0184\ \text{mm}^2$), macrophages (7 ± 11°), PLIA (20.2 ± 25.1% of all struts), and uncovered (3.0 ± 4.5) and malapposed (1.1 ± 2.2) struts.

More traditional endpoints examined included improved ABI, Rutherford class, minimal neointimal growth, and nitinol stent expansion with respect to baseline (35 ± 19%). We found comparable improvement in ABI (0.89 vs 0.86) and in mean Rutherford classification (1 vs 1) to the "Zilver-PTX Post-Market Study in Japan" clinical trial [23]. A study by Nishimura et al. measured vascular remodeling and stent expansion after implantation of self-expanding nitinol stents in the SFA using intravascular ultrasound [24]. They found a 41% increase in stent volume at 8-month follow-up, similar to the 35% increase at 12-month follow-up in the current study. Thus, the Zilver PTX stent performed in the current study as anticipated in the literature.

Recently, a meta-analysis conducted by Katsanos et al. has found that the use of paclitaxel-coated devices in femoral and popliteal arteries is associated with a higher all-cause mortality than drug-free devices at 2- and 5-years [13]. In the months following its publication, Katsanos' meta-analysis has felt some pushback from the scientific community. The primary criticisms of the meta-analysis have included that: (1) it provided no hypothetical rationale for an increased level of mortality resulting from paclitaxel exposure, which is especially odd inasmuch as the mortality divergence appears *after* the timespan in which paclitaxel would remain in the patients' systems, (2) it did not specify any cause of deaths (not having access to it), further compounding the

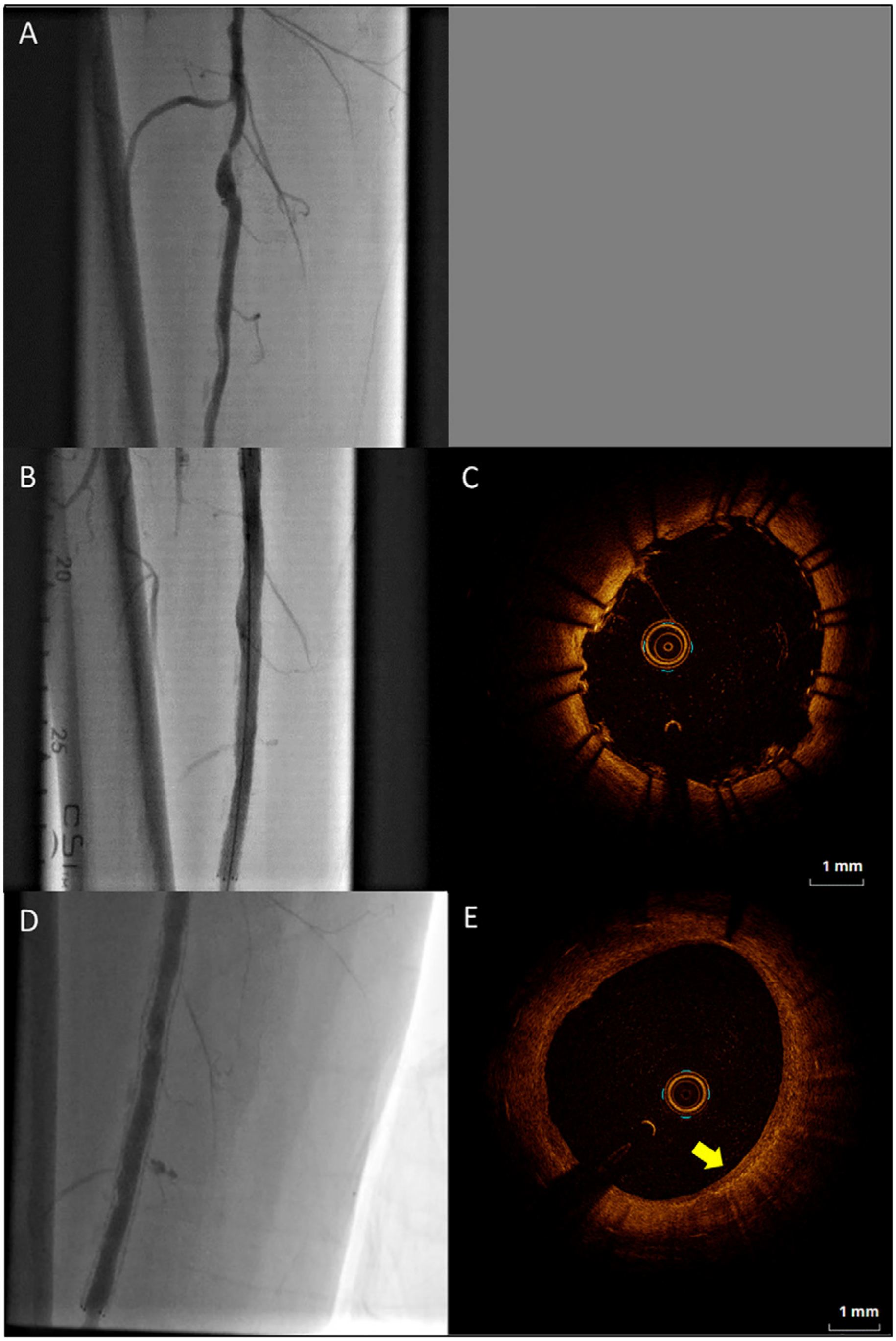

Fig. 1. Baseline angiography (A) of SFA stenosis. Angiography (B) and OCT (C) images immediately after Zilver PTX implantation. Angiography (D) and OCT (E) 12-month follow-up images. Note the presence of macrophage streaks (arrow) in (E).

ambiguity of mechanism, (3) it analyzed clinical trials whose purpose was to assess treatment efficacy rather than safety, and as such used intention-to-treat design that did not factor potential bias from patient cross-over and dropout, (4) it lacked access to individual clinical data, relying instead on published summaries, such that it was not possible to rigorously eliminate sources of potential bias in patient baseline characteristics, (5) it grouped balloons and stents (whether coated or uncoated) as a single homogenous class, despite differences in drug dosage vascular response between devices [25–28]. Beyond these criticisms, Katsanos' result has been contradicted by other meta-analyses [27,29], unpublished drug-coated balloon programs presented at the Leipzig Interventional Course [30–32], and analyses of Medicare claims data [33,34].

We believe the reported inflammatory markers observed by OCT may provide insight into the mechanism of the alleged link between paclitaxel and increased mortality reported by Katsanos et al. in a recent meta-analysis. Katsanos' findings are reminiscent of the findings of previous clinical trials of drug-eluting stents in the coronaries comparing outcomes of patients receiving paclitaxel vs other drug eluting stents. Though the SPIRIT IV trial showed higher rates of all-cause death in patients with PES than in patients with everolimus-eluting stents (EES), the COMPARE trial did not, and neither did the ENDEAVOR IV trial which compared PES to zotarolimus-eluting stents (ZES) [35–37]. However, all three trials showed significantly higher rates of myocardial infarction in the PES groups. A meta-analysis by Schömig et al. found that PESs in the coronaries resulted in higher rates of stent thrombosis

Table 1
Clinical characteristics of study population (n = 13).

Parameter	Unit	Baseline	12th month
Age	years	70.6 ± 10.3	N/A
Male	n (%)	8 (61.5)	N/A
Race			
Caucasian	n (%)	10 (77)	N/A
African-American	n (%)	3 (23)	N/A
6-min walk test (6MWT)	m	221.2 ± 79.5	248.3 ± 76.8[a]
Ankle Brachial Index		0.62 ± 0.17	0.89 ± 0.12[b]
Average Rutherford Class		3	1[b]
Angiography			
Target lesion length	cm	18.5 ± 13.2	N/A
Pre-procedural stenosis	%	86 ± 17	N/A
Residual stenosis	%	7 ± 18	N/A

6MWT: 6-min walk test.
Continuous and ordinal data are presented as the means ± standard deviation; nominal data are given as the counts (percentage).

[a] n = 12 since 1 patient refused 6MWT.

[b] Statistically significant difference between baseline and follow-up.

than sirolimus-eluting stents (SES) [38]. Imaging studies of DESs in the coronaries tell a similar story. First-generation DESs (including paclitaxel and sirolimus) show larger amounts of malapposition, uncovered struts, and intra-stent thrombus than second-generation DESs [39]. Implantation of PESs resulted in a higher frequency of PLIA than SESs [40,41]. A histopathological analysis of a diabetic coronary porcine model showed a higher degree of inflammation with PESs than EESs [42]. Our study represents an early description of a possible mechanism of paclitaxel inducing negative outcomes due to inflammation based on OCT endpoints in the SFA. Since Zilver PTX has no polymer and no carrier, it is appropriate to discuss these results as a response to the drug alone.

Paclitaxel induces apoptosis of medial smooth muscle cells [42–44], possibly by reduction of p-Akt, which leads to cellular debris and inflammatory response [45,46]. This increased inflammatory response has been measured in human thrombus aspirates [22], as well as histopathology of porcine models [42,47–50].However, since we have only measured indicators of inflammation and not traced any mechanism of how that would lead to the increased patient mortality seen by Katsanos, the link remains hypothetical.

We measured the presence of a variety of OCT markers of inflammation. Linear clusters of bright spots visualized in OCT are recognized as macrophages—a definitive marker of inflammation. PLIA can be described as dark areas surrounding struts in the OCT image. Sometimes they present as distinct regions surrounding an individual strut; other times, they present as a contiguous band encompassing an arc of struts or even the entire circumference of the stent. Histologically, they have been identified as hypocellular, atheromatous regions frequently infiltrated by macrophages [14–16]. Neovessels are also an indicator of inflammatory activity. Histological studies of patients undergoing carotid endarterectomy showed an association of macrophages, mast cells, and activated inflammatory cells with microvessel densities in excised tissue [17,19]. Poor strut coverage suggests inadequate vascular healing that could conceivably result from inflammatory presence. An autopsy study of AMI and stable angina patients found significantly more uncovered struts and inflammation in the culprit lesions of the AMI patients [20]. Likewise, an autopsy study of patients with either first- or second-generation DES showed that EES patients had significantly fewer uncovered struts and lower inflammation score than PES or SES patients [21]. The link between LST and inadequate strut endothelialization is well established [11]. The continued exposure of bare metal and polymers in the blood stream induces thrombosis. Therefore clots can be measured to assess the severity of inflammation.

Table 2
OCT data (n = 13).

Parameter	Unit	Value
Length of vessel stented	mm	201.1 ± 79.7
Neointima		
Neointimal area	mm^2	7.81 ± 3.84
Intra-patient standard deviation of neointimal area	mm^2	2.50 ± 0.86
Luminal narrowing	%	35.4 ± 18.2
Intra-patient standard deviation of luminal narrowing	%	10.9 ± 3.5
Maximal luminal narrowing	%	61.1 ± 25.0
Maximal luminal diameter narrowing	%	59.6 ± 19.3
Struts		
Baseline malapposition	%	10.3 ± 7.9[a]
12th month malapposition	%	1.1 ± 2.2[a]
Uncovered struts	%	3.0 ± 4.5
Struts with PLIA	%	20.2 ± 25.1
PLIA per strut	mm^2	0.017 ± 0.018
Stent cross-sectional area expansion from baseline	%	35 ± 19
Neovascularization		
Neovessels per mm stent	mm^{-1}	0.137 ± 0.181
Frames with neovessels	%	8 ± 10
Macrophage angle	degrees	7 ± 11
Thrombus area	mm^2	0.0093 ± 0.0184

PLIA: Peri-strut low-intensity area.
Data are presented as the means ± standard deviation.

[a] Statistically significant difference between baseline and follow-up ($p < 0.001$).

Others have shown evidence of OCT defined inflammation in response to paclitaxel. Previously, Kozuki et al. have compared tissue features between paclitaxel-eluting stents and bare metal stents in the SFA at 8-month follow-up [51]. They found significantly larger amounts of PLIA and macrophage accumulation with OCT as well as significantly smaller neointimal thickness and strut coverage rates in the paclitaxel stents. At 8-months, they found 4.0%, 2.4%, and 8.6 mm^2 uncovered struts, malapposition, and neointimal area, respectively, in their PES patients. At 12-months, we found 3.0%, 1.1%, and 7.81 mm^2, respectively. At 8-months, 46% and 13% of their PES patients had macrophages and thrombus, respectively. At 12-months, 61% and 46% of ours had macrophages and thrombus, respectively. Tomoi et al. have conducted an evaluation of vessel response to Zilver PTX implantation at 6 and 12 months [6]. We observed comparable values for neointimal area (7.8 vs 6.9 mm^2), luminal narrowing (35.4% vs 34.5%). However, we observed a smaller percentage of frames with neovessels at 12-months (8% vs 27%) as well as a smaller percentage of struts that were surrounded by PLIA (20% vs 44%). We also found a larger percentage of malapposed (1.1% vs 0.2%) and uncovered (3.0% vs 2.1%) struts at follow-up. Although Kozuki and Tomoi did not focus on inflammation, it is reassuring that our findings are supported in the literature.

Tosaka et al. have developed a classification scheme for femoropoliteal ISR based on a definition of restenosis as either >2.4 peak systolic velocity ratio by duplex scan or >50% stenosis by angiography. ISR is categorized as either class I, II, or III, respectively based on whether the lesion is a non-occluded stenosis <50 mm in length, a non-occluded stenosis >50 mm in length, or a total occlusion [52]. Applying this scheme with restenosis measured by OCT, 5 patients were class I, 1 patient was class II, and 1 excluded patient was class III, yielding an overall restenosis rate of 50%. Previously, the ZEPHYR and Zilver-PTX trials have examined the 12-month patency of femoropopliteal arteries implanted with PES. Both measured restenosis rates of 37% [23,53], similar to our findings.

4.1. Study limitations

First, this was a single-center study and included a small study population with a high rate of patient dropout. Second, this OCT defined inflammatory study lacked any control group, so we make no statement that Zilver PTX shows better or worse inflammatory response than any other SFA stent. Third, the OCT system was designed for imaging of coronary arteries, which have much smaller diameters than SFAs. This meant that sometimes a catheter abutted against the vessel wall might not be able to image the other side of the vessel if the vessel has a relatively large lumen. The necessity of excluding such segments from analysis biases our results toward larger values of neointimal growth. Fourth, the measurement of PLIA is inherently subjective, because its contours are delineated by a change in the intensity of the OCT signal. However, signal intensity is also a function of tissue depth, which means it becomes more difficult to see whether there is PLIA around struts buried deeply in neointima. Since many such struts must be excluded for this reason, the PLIA measurements could be biased. Fifth, because this study protocol was originally conceived as a patency and apposition assessment rather than an immunologic assessment, serology and time points >1 year were never included. Katsanos found significant differences of death rate at 2- and 5- year time points, but not at the 1-year time point examined in the current study.. Sixth, though we have shown literature and OCT evidence of paclitaxel-induced inflammation, we make no statement as to how the inflammation could be linked to worse clinical outcomes.

5. Conclusion

We have identified and measured several OCT markers of inflammation including macrophage arc, strut coverage, neovascularization, PLIA, and thrombus. These are important metrics for characterizing vascular response to local interventional devices because it is known that inflammation leads to stent thrombosis.

Data accessibility statement

Study data have been uploaded to [Figshare: https://doi.org/10.6084/m9.figshare.7883345] and will be available on March 22nd, 2020.

Declaration of Competing Interest

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